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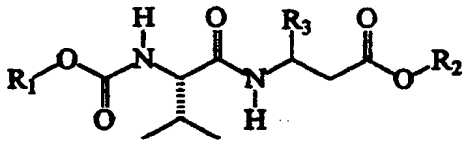
(54) Dipeptide compounds having fungicidal activity and their agronomic use

(57) The invention relates to dipeptide compounds having formula (I):



(I)

- The compounds having formula (I) have a high antifungal activity and are used for the control of phytopathogens in the agronomic field.

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Description

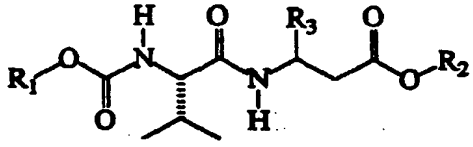
[0001] The present invention relates to new dipeptide compounds capable of controlling phytopathogens which cause considerable economic damage to agricultural crops.

[0002] More specifically, the present invention relates to new dipeptide compounds capable of effectively controlling phytopathogens of crops of great economic interest, such as, for example, vines, potatoes and tobacco, as well as their agronomic use, alone or mixed with one or more active principles with a fungicidal activity, and the process for their preparation.

[0003] The patent application EP 652 229 A2 discloses suitably functionalized oligopeptide compounds having a high fungicidal activity consisting of one or two aliphatic amino acids, such as valine, leucine and isoleucine, conjugated to one or two aromatic amino acids, such as phenylglycine, phenylalanine and β-phenylalanine (or 3-amino-3-phenyl-propanoic acid), whose free amine and carboxyl functions can also be suitably functionalized.

[0004] Patent application EP 718 280 A2 again describes compounds based on 3-amino-3-arylpropanoic acids suitably substituted. Among the compounds based on 3-amino-3-arylpropanoic acids claimed, there are also dipeptide compounds obtained by means of bonds between the amine group of said 3-amino-3-arylpropanoic acids and the carboxyl group of an amino acid, such as valine appropriately functionalized on its amine function.

[0005] Said patent applications EP 652 229 A2 and EP 718 280 A2, among the numerous examples which illustrate the invention, describe dipeptide compounds, whose basic skeleton consists of L-valine conjugated by means of its carboxyl group with an aromatic β-amino acid (3-amino-3-aryl-propanoic acid) and whose structures can be defined by a single general formula (Ia):



(Ia)

wherein:

- R_1 represents a linear or branched C_1-C_8 alkyl group, or a phenyl group;
- R_2 represents a linear or branched C_1-C_8 alkyl group;
- R_3 can be a phenyl group optionally substituted.

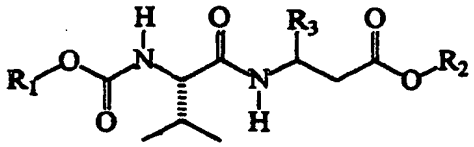
[0006] On the basis of what is described in the above patent applications, these dipeptide compounds are particularly effective in the control of Oomycetes.

[0007] The products specified which can be defined by this general formula are generally characterized by the functionalization of the amine residue with a carboxy-tertbutyl group (R_1 therefore means tert-butyl) or by the esterification of the carboxyl residue with an alkyl group, and the R_2 group therefore has the meaning of a methyl, ethyl and isopropyl group, in the presence of an R_3 phenyl group.

[0008] The compounds having general formula Ia also allow synergic fungicidal mixtures to be obtained with the levorotatory isomer of methyl (N-phenylacetyl-N-2,6-xylyl)alaninate (Benalaxyl), as described in the patent WO 98 26654 A2.

[0009] The Applicant has now found that new dipeptide compounds having formula (I), which have never been described before, have a higher fungicidal activity than those of the dipeptide compounds specified in the known art.

[0010] The present invention therefore relates to dipeptide compounds having formula (I):



(I)

wherein:

- R_1 represents an isopropyl or phenyl group;
- R_2 represents a methyl group;
- R_3 can be a phenyl group substituted in position 4 with an R_4 group; or it can represent a 2-benzothiazole group, optionally substituted with an R_5 group;
- R_4 and R_5 can be a fluorine or chlorine atom; a methyl or ethyl group; or a methoxyl group; or they can represent a cyano group.

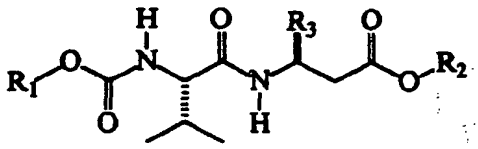
[0011] The configuration of the atom of the valine residue present in all compounds having formula (I) is S, according to the Cahn, Ingold and Prelog convention.

[0012] The absolute configuration of the chiral atom of aromatic β-amino acid incorporated in the dipeptide compound may, on the contrary, be either S or R.

[0013] The compounds of the present invention, considering jointly the asymmetrical centres present in the molecule, may be in diastereoisomeric forms S-S or S-R, wherein the first letter refers to the chiral centre of valine whereas the second letter describes the chiral centre of aromatic β-amino acid, or they can be present as a diastereoisomeric mixture in which the two forms are in any molar ratio.

[0014] The Applicant has found that compounds in which the absolute configuration of the chiral atom of aromatic β-amino acid incorporated in the dipeptide compound is R, have a greater fungicidal activity.

[0015] A particular aspect of the present invention therefore relates to dipeptide compounds having formula (I) wherein the absolute configuration of the chiral atom of the β-amino acid residue is R, as represented by general formula (II)



(II)

wherein:

- R_1, R_2, R_3 have the meaning defined above (formula I).

[0016] The compounds of the present invention can be conveniently used in agriculture as a diastereoisomeric mixture in which the two forms can be present in any molar ratio.

[0017] According to present conventions, a compound having formula (I) with an epimeric form S-RS contains these diastereoisomeric forms S-S and S-R in an equimolecular ratio.

[0018] Owing to the higher activity of compounds in which the absolute configuration of the chiral atom of aromatic β-aminoacid is R, the compounds having formula (I) are preferably used as a diastereoisomeric mixture in which the diastereoisomeric form S-R is greater than 80%.

[0019] Even more preferable are diastereoisomeric mixtures in which the diastereoisomeric form S-R is present in greater quantities, such as, for example, diastereoisomeric mixtures containing the form S-R in quantities exceeding 90%, 95% or 98%.

[0020] The use of compounds having formula (I) in the sole diastereoisomeric form S-R, is the most preferable.

[0021] The compounds having formula (I) can be used alone or optionally associated with at least one other compound having a fungicidal activity.

[0022] The present invention therefore relates to fungicidal compositions comprising:

a) a dipeptide compound having formula (I) as a diastereoisomeric mixture in which the two forms can be present in any molar ratio, or as a sole diasatereoisomeric form S-R;
b) one or more fungicides selected from:

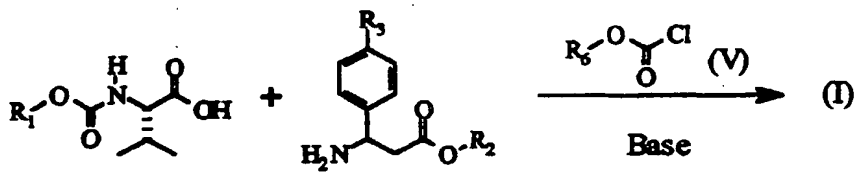
(1) Cymoxanil corresponding to 1-(2-cyano-2-methoxyimino-acetyl)-3-ethylurea;
(2) Fosetyl-Al corresponding to the aluminum salt of ethyl hydrogen phosphonate;
(3) Potassium phosphonate;
(4) Benalaxyl corresponding to methyl N-(phenylacetyl)-N-2,6-xylyl-RS-alaninate;
(5) Methyl N-(phenylacetyl)-N-2,6-xylyl-R-alaninate;

(6) Metalaxyl corresponding to methyl N-(2-methoxyacetyl)-N-2,6-xylyl-RS-alaninate;
(7) Mefenoxam corresponding to methyl N-(2-methoxyacetyl-N-2,6-xylyl-R-alaninate;
(8) Oxadixyl corresponding to 2-methoxy-N-(2-oxo-1,3-oxazolidin-3-yl)acet-2',6'-xylidinide;
(9) Ofurace corresponding to DL-3-(N-chloroacetyl-N-(2,6-xylyl)-amino]-γ-butyrolactone;
(10) Iprovalicarb corresponding to O-(1-methylethyl)-N-(2-methyl-1-[[[1-(4-methylphenyl)ethyl]amino]carbonyl]propyl]carbamate;
(11) Azoxystrobin corresponding to methyl (E)-2-[2-(6-(2-cyanophenoxy)-pyrimidin-4-yloxy]phenyl]-3-methoxyacrylate;
(12) Kresoxym-methyl corresponding to methyl (E)-methoxyimino-α-[o-tolyloxy)-o-tolyl]acetate;
(13) Metominofen corresponding to the experimental abbreviation SSF-126 and corresponding to N-methyl-(E)-methoxyimino-(2-phenoxyphenyl)acetamide;
(14) Acylbenzolar corresponding to methylbenzothiadiazole-7-thiocarboxylate;
(15) Famoxadone corresponding to 5-methyl-5-(4-phenoxyphenyl)-3-(phenylamino)oxazolidin-2,4-dione;
(16) Fenamidone corresponding to 4-methyl-4-phenyl-1-(phenylamino)-2-methylthioimidazolidin-5-one;
(17) IKF916 corresponding to 2-cyano-4-chloro-5-(4-methylphenyl)-1-(N,N-dimethylaminosulfamoyl)imidazole;
(18) Fluazinam corresponding to 3-chloro-N-(3-chloro-5-trifluoromethyl-2-pyridyl)-α,α,α-trifluoro-2,6-dinitro-p-toluidine;
(19) Dimethomorph corresponding to (E,Z)-4-[3-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl)acryloyl] morpholine;
(20) Flumetover corresponding to N,N-diethylamide of 4-trifluoromethyl-6-(3,4-dimethoxyphenyl)benzoic acid;
(21) Chlorothalonil corresponding to 1,3-dicyano-2,4,5,6-tetrachlorobenzene;
(22) Thiram corresponding to *bis*-(dimethylthiocarbamoyl)disulfide (polymer);
(23) Propineb corresponding to the zinc salt of propylene*bis*(dithiocarbamate) (polymer);
(24) Mancozeb corresponding to the manganese and zinc salt of ethylene*bis*(dithiocarbamate)(polymer);
(25) Maneb corresponding to the manganese salt of ethylene*bis*(dithiocarbamate) (polymer);
(26) Zineb corresponding to the zinc salt of ethylene*bis*(dithiocarbamate) (polymer);
(27) Dichlofluanide corresponding to N-dichlorofluoromethylthio-N',N'-dimethyl-N-phenylsulfamide;
(28) Tolylfluanide corresponding to N-dichlorofluoromethylthio-N',N'-dimethyl-N-p-tolylsulfamide;
(29) Captano corresponding to N-(trichloromethylthio)cyclohex-4-ene-1,2-dicarboxyimide;
(30) Folpet corresponding to N-(trichloromethylthio)phthalimide;
(31) Dithianon corresponding to 5,10-dihydro-5,10-dioxonaphthol[2,3-b]-1,4-dithi-in-2,3-dicarbonitrile;
(32) Etridiazole corresponding to ethyl-3-trichloromethyl-1,2,4-thiadiazolyl ether;
(33) Hymexanol corresponding to 5-methylisoxazol-3-ole;
(34) Protiocarb corresponding to S-ethyl-(3-dimethylaminopropyl)thiocarbamate;
(35) Propamocarb corresponding to propyl-(3-dimethylaminopropyl)carbamate;
(36) A copper (I) salt or copper (II) salt, such as copper oxychloride, copper hydroxide, or copper sulfate;
(37) Mepanipyrim corresponding to N-(4-methyl-6-prop-1-inylpyrimidin-2-yl)aniline;
(38) Pirymethanil corresponding to N-(4,6-dimethylpyrimidin-2-yl)aniline;
(39) Cyprodinil corresponding to N-(4-methyl-6-cyclopropylpyrimidin-2-yl)aniline;
(40) R-3-aminobutanoic acid or RS-3-aminobutanoic acid.

[0023] The compounds having formula (I) can be obtained by means of numerous synthetic methods.

[0024] For merely illustrative but non-limiting purposes, schemes A and B indicate some preparations of compounds having formula (I) wherein R_1, R_2 and R_3 have the meanings already defined in the description of general formula (I).

Scheme A:

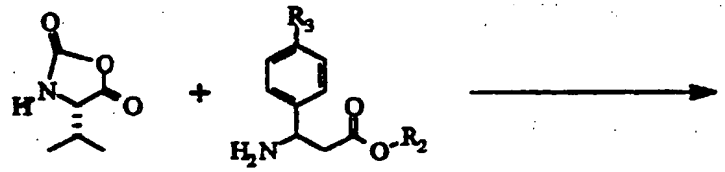


(III) (IV) (V) (I)

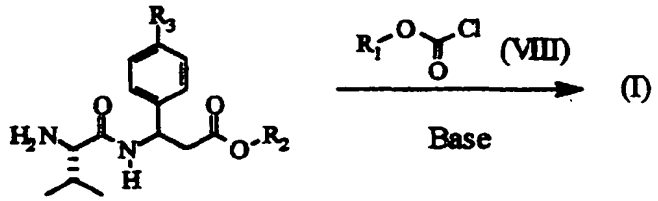
Base

[0025] The carbamate (III) is reacted with an organic base, such as N-methylmorpholine, triethylamine, or N,N-dimethylbenzylamine, in an organic solvent such as dichloromethane, or ethyl acetate, or toluene, at a temperature ranging from -40°C to 25°C. Alkyl chloroformiate (V) is then added, wherein R_6 has the meaning of a linear or branched C_1-C_8 alkyl group, such as for example, methyl, ethyl, isopropyl, isobutyl, the temperature being maintained within a range of -40C to 25°C. The ester (IV), optionally diluted in the reaction solvent, is then added, the temperature being maintained within a range of -40°C to 30°C, obtaining the desired compound having formula (I).

Scheme B:



(VI) (IV)



(VII) (VIII) (I)

Base

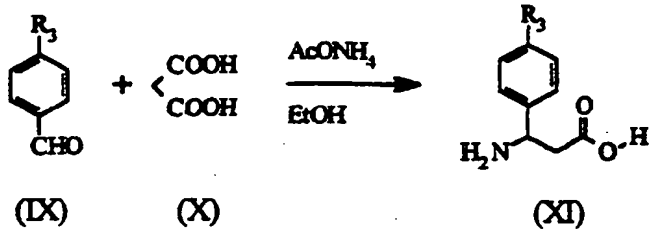
The ester (IV) is reacted with the anhydride (VI), whose preparation is described for example in "Berichte" (1906), Vol. 39, page 857 or in "Journal of Chemical Society" (1950), page 3213 and page 3461, in an organic solvent, such as dichloromethane, trichloromethane, ethyl acetate or tetrahydrofuran, in the presence of or without an organic base, such as triethylamine or N-methyl-N,N-dioctylamine, at a temperature ranging from -80°C to room temperature, as described for example in "Journal of Chemical Society" (1950), page 3461. The dipeptide (VII) thus obtained is reacted, for example, in an organic solvent, such as dichloromethane or ethyl acetate, with the chloroformiate (VIII) in the presence of an inorganic base, such as sodium bicarbonate or potassium carbonate, or in the presence of an organic base, such as triethylamine, pyridine, N-methylmorpholine, N,N-dimethylbenzylamine, at a temperature ranging from -40°C to

30°C, to obtain the desired compound having formula (I).

[0026] The carbamate (III) can be easily prepared by the addition of an alkylchloroformiate (VIII) to an aqueous solution of L-valine, in the presence of an inorganic base, such as sodium bicarbonate, potassium carbonate or sodium hydroxide, or an organic base such as triethylamine, at a temperature ranging from 0°C to 25°C; or by the addition of chloroformiate (VIII) to a solution of silanized L-valine, prepared "in situ" using the conditions described, for example, in "Berichte" (1967), Vol. 100, page 1638 or in "Berichte" (1970), Vol. 103, page 3353.

[0027] The racemic ester having formula (IV) can be obtained according to Scheme C below:

Scheme C



(IX) (X) (XI)

(XI) (IV)

[0028] A suitable para-substituted benzaldehyde (IX) is reacted with malonic acid (X) in the presence of an ammonium salt, such as ammonium acetate or ammonium propionate, in a protic solvent, such as methyl alcohol, ethyl alcohol or ethylene glycol, at a temperature ranging from 40°C to the boiling point of the pre-selected solvent, to obtain the desired β-amino acid (XI).

[0029] The β-amino acid (XI) thus obtained is transformed into methyl ester (VI) by means of one of the methods known in literature for the esterification of α-amino acids, for example, using solutions of a mineral acid, such as sulfuric acid or hydrochloric acid, or an organic acid, such as methanesulfonic acid or para-toluenesulfonic acid, in methanol, at a temperature ranging from room temperature to the boiling point of the solvent mixture; or by reacting said acid (XI) in methanol in the presence of equimolecular quantities or with an excess of thionyl chloride, at a temperature ranging from 20°C to the boiling point of the solvent mixture.

[0030] In order to obtain compounds having formula (I) as a diastaereoisomeric mixture in which one of the diastereoisomeric forms is greater than 50%, an ester having formula (IV), in which one of the enantiomeric forms is greater than 50%, was obtained by the fractional crystallization of the salt formed by the reaction of the racemic ester (IV) with a suitable, optically active acid, such as tartaric acid, camphorsulfonic acid, O-(N-phenylaminocarbonyl)lactic acid, or an N-alkoxycarbonyl-α-amino acid.

[0031] Other methods for obtaining an ester having formula (IV) in an optically active form use an enantioselective, enzymatic hydrolysis of the racemic ester (IV) to obtain, depending on the enzyme used, the ester (IV) or acid (XI) in the desired enantiomeric form. The optically active acid (XI) is subsequently transformed into the required ester (IV) in the desired enantiomeric form, by one of the esterification methods already described for transforming the racemic acid (XI) into the racemic ester (IV).

Compound (I) is described in "The Pesticide Manual", 1983, VIIth edition, British Crop Protection Council Ed., page 148.

Compound (2) is described in "The Pesticide Manual", 1983, VIIth edition, British Crop Protection Council Ed.,

page 294.
Compound (3) is easily available on the market.
Compound (4) is described in "The Pesticide Manual", 1983, VIIth edition, British Crop Protection Council Ed., page 32.
Compound (5) is described in patent application WO 98 26654 A2.
Compound (6) is described in English patent GB 1,500,581.
Compound (7) is described in patent application WO 96 01559 A1.
Compound (8) is described in English patent GB 2,058,059.
Compound (9) is described in "Phytopatological News" (1978), Vol. 9, page 142.
Compound (10) is described in patent applications EP 610,764 and EP 550,788.
Compound (11) is described in European patent application EP 382,375.
Compound (12) is described in European patent application EP 253,213.
Compound (13) is described in American patent US 5,185,242.
Compound (14) is described in American patent US 4,931,581.
Compound (15) is described in "Brighton Crop Protection Conference - Pests and Diseases" (1996), Congress Acts.
Compound (16) is described in European patent application EP 629,616.
Compound (17) is described in European patent application EP 705,823.
Compound (18) is described in European patent application EP 31,257.
Compound (19) is described in European patent application EP 219,756.
Compound (20) is described in European patent applications EP 360,701 and EP 611,232.
Compound (21) is described in "The Pesticide Manual", 1983, VIIth edition, British Crop Protection Council Ed., page 120.
Compound (22) is described in "The Pesticide Manual", 1983, VIIth edition, British Crop Protection Council Ed., page 534.
Compound (23) is described in "The Pesticide Manual", 1983, VIIth edition, British Crop Protection Council Ed., page 469.
Compound (24) is described in "The Pesticide Manual", 1983, VIIth edition, British Crop Protection Council Ed., page 339.
Compound (25) is described in "The Pesticide Manual", 1983, VIIth edition, British Crop Protection Council Ed., page 340.
Compound (26) is described in "The Pesticide Manual", 1983, VIIth edition, British Crop Protection Council Ed., page 569.
Compound (27) is described in "The Pesticide Manual", 1983, VIIth edition, British Crop Protection Council Ed., page 175.
Compound (28) is described in "The Pesticide Manual", 1983, VIIth edition, British Crop Protection Council Ed., page 537.
Compound (29) is described in "The Pesticide Manual", 1983, VIIth edition, British Crop Protection Council Ed., page 87.
Compound (30) is described in "The Pesticide Manual", 1983, VIIth edition, British Crop Protection Council Ed., page 599.
Compound (31) is described in "The Pesticide Manual", 1983, VIIth edition, British Crop Protection Council Ed., page 225.
Compound (32) is described in "The Pesticide Manual", 1983, VIIth edition, British Crop Protection Council Ed., page 252.
Compound (33) is described in "The Pesticide Manual", 1983, VIIth edition, British Crop Protection Council Ed., page 314.
Compound (34) is described in "The Pesticide Manual", 1983, VIIth edition, British Crop Protection Council Ed., page 473.
Compound (35) is described in "The Pesticide Manual", 1983, VIIth edition, British Crop Protection Council Ed., page 471.
Compounds (36) are easily available on the market.
Compounds (37), (38) and (39) are described in "Pesticide Science" (1996), Vol. 47, pages 191-197.
Compound (40) is described in patent application WO 95 15684.

[0032] The fungicidal compositions comprising these compounds having formula (I) alone or mixed with one or more products (1)-(40), object of the present invention, have a high fungicidal activity with respect to numerous fungine species. Examples of pathogens controlled by the above compositions, and also examples of application crops, are pro-

vided hereunder for illustrative purposes only, without there being any limitations whatsoever:

Plasmopara viticola (vines);
Phytophtora infestans (tomatoes, potatoes);
Phytophtora nicotianae (tobacco, ornamental plants);
Phytophtora palmivora (cocoa);
Phytophtora cinnamomi (pineapples, citrus fruit);
Phytophtora capsici (peppers, tomatoes, cucurbitaceae);
Phytophtora cryptogea (tomatoes, plums, ornamental plants);
Phytophtora megasperma (ornamental plants);
Phytophtora citri (citrus fruit);
Peronospora tabacina (tobacco);
Pseudoperonospora cubensis (cabbages, cucurbitaceae);
Pseudoperonospora humili (hops);
Bremia (salad).

[0033] The compositions object of the present invention are capable of carrying out a high fungicidal action, allowing preventive, protective, prophylactive, systemic, curative and eradicative treatment to be applied.

[0034] The compositions object of the present invention can be used in different quantities depending on the crop, pathogen, environmental conditions and type of formulation adopted.

[0035] The application doses per hectare of compound having formula (I) are generally within the range of 5-500 g, whereas those of the possible compounds (1)-(40) present in the composition, are within the range of 5-3500 g.

[0036] The compositions object of the present invention can be applied to any part of the plant, for example leaves, stalks, branches and roots, or on the seeds themselves before sowing, or even on the ground where the plant grows.

[0037] The compositions object of the present invention are used in agronomic practice as compositions in various forms such as for example: dry powders, wettable powders, emulsifiable concentrates, micro-emulsions, pastes, granulates, solutions, suspensions, etc. The selection of the type of composition depends on the specific use.

[0038] The compositions are prepared with known methods, for example by diluting or dissolving the active substance with a solvent medium and/or a solid diluent, optionally in the presence of surface-active agents.

[0039] Solid diluents or carriers which can be used are: silica, kaolin, bentonite, talc, fossil flour, dolomite, calcium carbonate, magnesia, chalk, clays, synthetic silicates, attapulgite, sepiolite.

[0040] Various solvents, for example aromatics (xylols or mixtures of alkylbenzols), paraffins (petroleum fractions), alcohols (methanol, propanol, butanol, octanol, glycerine), amines, amides (N,N-dimethylformamide, N-methylpyrrolidone), ketones (cyclohexanone, acetone, acetophenone, isophorone, ethylamylketone), esters (isobutyl acetate, methyl esters of fatty acids obtained for example by the transesterification of vegetable oils), can be used as liquid diluents, in addition to water naturally.

[0041] Surface-active agents which can be used are salts of sodium, calcium, triethanolamine, or triethylamine of alkyl sulfonates, alkylarylsulfonates, polyethoxylated alkylphenols, fatty alcohols condensed with ethylene oxide, polyoxyethylated fatty acids, polyoxyethylated esters of sorbitol, ligninsulfonates.

[0042] The compositions can also contain special additives for particular purposes such as, for example, adhesive agents, such as Arabic rubber, polyvinyl alcohol, polyvinylpyrrolidone.

[0043] The concentration of active substances in the above compositions varies from 0.1% to 98%, preferably from 0.5% to 90%.

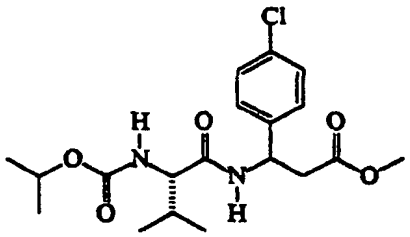
[0044] If desired, it is possible to also add other compatible active principles to the compositions object of the present invention, such as for example, phytoregulators, antibiotics, herbicides, insecticides, fertilizers.

[0045] The following examples are provided for illustrative purposes and do not limit the scope of the present invention.

EXAMPLE 1:

(a) Preparation of methyl (±) RS-[3-(N-isopropoxycarbonyl-S-valinyl)amino]-3-(4-chlorophenyl)propanoate (*epimeric form S-RS)* (Compound Nr. 1)

[0046]



[0047] N-methylmorpholine (cm^3 187) is added to a solution of N-isopropoxycarbonyl-S-valine (345 g) in trichloromethane (cm^3 2300), cooled to -15÷-10°C, followed, after about 15' and at a temperature of -40÷-35°C, by a solution of isobutylchloroformiate (cm^3 221) in trichloromethane (cm^3 300). After about 30' and maintaining the same temperature, a solution of methyl RS-3-amino-3-(4-chlorophenyl)propanoate (360 g) in trichloromethane (cm^3 600) is added dropwise. After letting the temperature rise to room values, the reaction is left under stirring for a night. Water (cm^3 1400) is then added, which, after removing the organic phase, is extracted with trichloromethane (cm^3 500 x 2 times). The organic phases are joined and washed with water (cm^3 800 x 4), then dried on sodium sulfate and concentrated to a minimum volume at reduced pressure. The solution thus obtained is poured into a large volume of hexane maintained under vigorous stirring. The white crystal which is separated is collected by filtration, then washed with additional hexane, to obtain, after drying in air, 630 g of the desired product, for a yield of 94%.

[0048] The physico-chemical characterization of compound Nr. 1 gave the following results:

$[\alpha]_D^{25°C}$(C = 1, CH_2Cl_2) = -12.5°
GC-MS: 398 (M^+), 212, 158, 116 (100%), 72
Elemental analysis [% found (theoretical)] =
C 52.4 (52.21); H 6.80 (6.82); N 7.05 (7.02); Cl 8.85 (8.89).

b) Preparation of methyl (±)RS-3-amino-3-(4-chlorophenyl) propanoate.

[0049] Thionyl chloride (304 g) is slowly added dropwise to a suspension of (±)RS-3-amino-3-(4-chlorophenyl)propanoic acid (507 g) in methanol (cm^3 3000) maintained under vigorous stirring, the exothermy being controlled by means of the addition rate. The solution thus obtained is refluxed for about 8 hours and then concentrated to minimum volume. Water (cm^3 1500) is added to the oil obtained, and is then extracted with ethyl ether (cm^3 1000) and then basified with potassium carbonate until pH 8 is reached. The base aqueous solution thus obtained is extracted with ethyl acetate (cm^3 700 x 3 times) and the organic phases are joined, dried on sodium sulfate and then evaporated at reduced pressure. The desired product is obtained (491 g) for a yield of 91%.

GC-MS: 213 (M^+), 198, 153, 140 (100%), 113, 77.

c) Preparation of (±)RS-3-amino-3-(4-chlorophenyl)propanoic acid.

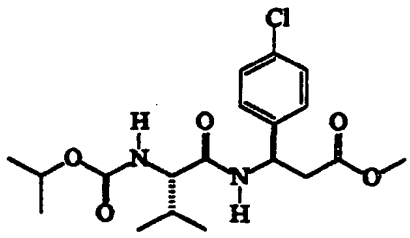
[0050] A suspension of malonic acid (530 g), 4-chlorobenzaldehyde (666 g) and ammonium acetate (590 g) in ethanol (cm^3 1500) is brought to reflux temperature under vigorous stirring for about 8 hours. The reaction mixture initially becomes limpid and then produces a constantly increasing precipitate. After cooling the whole mixture to room temperature, the crystal obtained is filtered (805 g) obtaining the desired product with a yield of 85%.

Elemental analysis [% found (theoretical)]=
C 54.01 (54.15); H 5.10 (5.05); N 7.12 (7.02); Cl 17.80 (17.76).

EXAMPLE 2

a) Preparation of methyl (±)R-[3-(N-isopropoxycarbonyl-S-valinyl)amino]-3-(4-chlorophenyl)propanoate (*diastereoisomeric form S-R)* (Compound Nr. 2)

[0051]



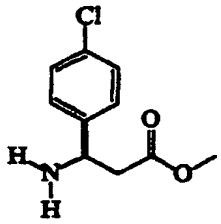
[0052] Compound Nr. 2 was obtained with a procedure and preparative scale analogous to that described in example 1, starting from an ester enriched in the enantiomeric form methyl R-3-amino-3-(4-chlorophenyl)propanoate (e.e. 80%, calculated by HPLC, using a chiral column) with an overall yield of 96%.

[0053] The physico-chemical characterization of compound Nr. 2 gave the following results:

Enantiomeric composition [S-R:S-S] (HPLC), chiral column = [80:20]
$[\alpha]_D^{25°C}$ (C = 1, CH_2Cl_2) = +4.4°
GC-MS: 398 (M^+), 212, 158, 116 (100%), 72
Elemental analysis [% found (theoretical)] =
C 52.23 (52.21); H 6.83 (6.82); N 7.04 (7.02); Cl 8.90 (8.89).

b) Preparation of methyl (+)R-3-amino-3-(4-chlorophenyl) propanoate.

[0054]



[0055] L-tartaric acid (35 g) is added to a solution of the ester methyl (±)RS-3-amino-3-(4-chlorophenyl)propanoate in methanol (cm^3 500). The solution which, under vigorous stirring, becomes limpid accompanied by a slight exothermy, is then brought to -10°C. The type of crystal is examined: in the case of the formation of vaporous crystals (racemic crystal) the solution is redissolved by diluting with additional methanol, until compact crystalline seeds are obtained on the bottom of the container.

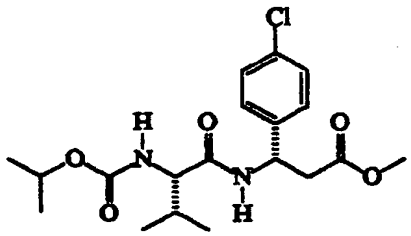
[0056] After about 72 hours the precipitate is rapidly filtered, washed with ethyl ether and dried in air. The salt thus obtained (25 g) is dissolved in water to which potassium carbonate (26 g) is added and which is then extracted three times with dichloromethane. The organic phases joined and dried on sodium sulfate are evaporated at reduced pressure to obtain the desired product (15.2 g) for a yield of 60%.

$[\alpha]_D^{25°C}$ (C = 1, CH_2Cl_2) = +10°
Enantiomeric composition [S-R: S-S] (HPLC), chiral column = [80:20]

EXAMPLE 3

a) Preparation of methyl (-)S-[3-(N-isopropoxycarbonyl-S-valinyl)amino]-3-(4-chlorophenyl)propanoate *(diastereoisomeric form S-S)* (Compound Nr. 3)

[0057]



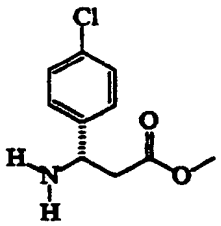
[0058] Compound Nr. 3 was obtained with a procedure and preparative scale analogous to that described in example 1, starting from an ester enriched in the enantiomeric form methyl S-3-amino-3-(4-chlorophenyl)propanoate (e.e. 90%, calculated by HPLC, using a chiral column) with an overall yield of 91%.

[0059] The physico-chemical characterization of compound Nr. 3 gave the following results:

Enantiomeric composition [S-R: S-S] (HPLC), chiral column = [10:90]
$[\alpha]_D^{25°C}$ (C = 1, CH_2Cl_2) = -24.4°
GC-MS: 398 (M^+), 212, 158, 116 (100%), 72
Elemental analysis [% found (theoretical)] =
C 52.21 (52.21); H 6.81 (6.82); N 6.99 (7.02); Cl 8.88 (8.89).

b) Preparation of methyl (-)S-3-amino-3-(4-chlorophenyl) propanoate

[0060]



[0061] Compound Nr. 3 was obtained with a procedure and preparative scale analogous to that described in example 2 for the preparation of the ester methyl R-3-amino-3-(4-chlorophenyl)propanoate, but using D-tartaric acid as resolvent agent, with a yield of 48%.

Enantiomeric composition [S-R: S-S] (HPLC), chiral column = [10:90]

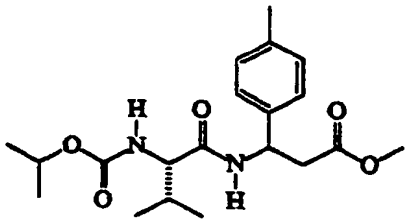
$[\alpha]_D^{25°C}$ (C = 1, CH_2Cl_2 = - 9.6°

EXAMPLE 4

[0062] Using preparative procedures analogous to those described in the previous examples, the following com-

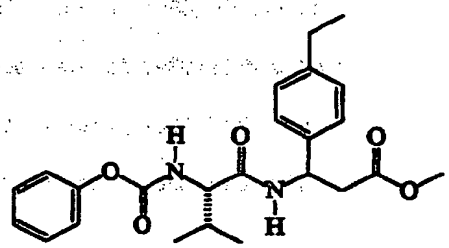
pounds indicated together with their chemical characterization, were prepared:

- methyl RS-[3-(N-isopropoxycarbonyl-S-valinyl)amino]-3-(4-methylphenyl)propanoate *(epimeric form S-RS)* (Compound Nr. 4)



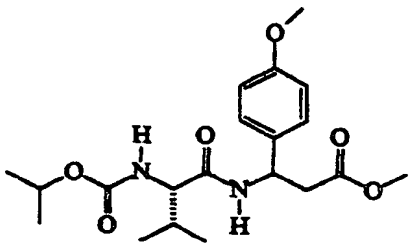
$[\alpha]_D^{25°C}$(C = 1, CH_2Cl_2) = - 10.7°
Elemental analysis [% found (theoretical)] =
C 63.42 (63.47); H 7.89 (7.99); N 7.33 (7.40).

- methyl RS-[3-(N-phenoxycarbonyl-S-valinyl)amino]-3-(4-ethylphenyl)propanoate *(epimeric form S-RS)* (Compound Nr. 5)



Elemental analysis [% found (theoretical)] =
C 67.49 (67.59); H 6.99 (7.09); N 6.59 (6.57).

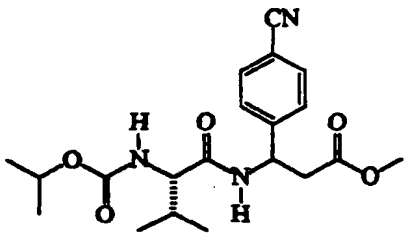
- methyl RS-[3-(N-isopropoxycarbonyl-S-valinyl)amino]-3-(4-methoxyphenyl)propanoate *(epimeric form S-RS)* (Compound Nr. 6)



Elemental analysis [% found (theoretical)] =

C 60.96 (60.90); H 7.22 (7.67); N 7.23 (7.10).

- methyl RS-[3-(N-isopropoxycarbonyl-S-valinyl)amino]-3-(4-cyanophenyl)propanoate *(epimeric form S-RS)* (Compound Nr. 7)

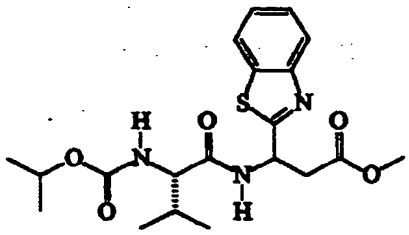


$[\alpha]_D^{25°C}$ (C = 1, CH_2Cl_2) = - 11.9°
Elemental analysis [% found (theoretical)] =
C 61.70 (61.68); H 7.02 (6.99); N 10.72 (10.79).

EXAMPLE 5

a) Preparation of methyl (±)RS-[3-(N-isopropoxycarbonyl-S-valinyl)amino-3-(benzothiazol-2-yl)propanoate *(epimeric form S-RS)* (Compound Nr. 8)

[0063]



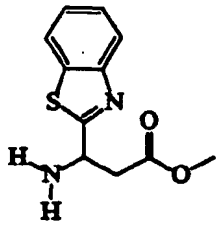
[0064] Compound Nr. 8 was obtained with a procedure and preparative scale analogous to that described in example 1, starting from an ester methyl RS-3-amino-3-(benzothiazol-2-yl)propanoate with an overall yield of 74%.

[0065] The physico-chemical characterization of compound Nr. 8 gave the following results:

Elemental analysis [% found (theoretical)] =
C 56.91 (56.99); H 6.42 (6.46); N 10.03 (9.97); S 7.55 (7.61).

b) Preparation of methyl (±)RS-3-amino-3-(benzothiazol-2-yl) propanoate

[0066]



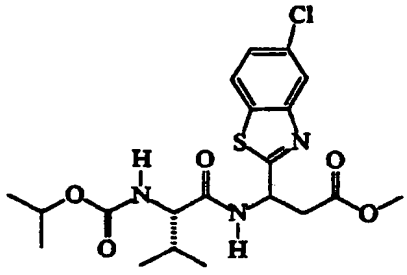
[0067] Methyl γ-ester hydrochloride of aspartic acid (500 g) and phosphorous oxychloride (cm^3 250) are added, in order, to a solution of 2-aminothiophenol (337 g) in toluene (cm^3 2500). The reaction is refluxed for about 20', with the formation of rubbery masses. The liquid phase is decanted, an aqueous solution of sodium hydroxide is added and the solution thus obtained is extracted with ethyl acetate. The organic phase is evaporated at reduced pressure and the oil obtained is crystallized with ethyl ether. An impure yellow solid is obtained, which is used directly for the previous reaction without any further purification.

GC-MS: 236(M^+), 163 (100%), 136, 102, 70

EXAMPLE 6

a) Preparation of methyl (±)RS-[3-(N-isopropoxycarbonyl-S-valinyl)amino]-3-(5-chlorobenzothiazol-2-yl)propanoate (*epimeric form S-RS*) (Compound Nr. 9)

[0068]



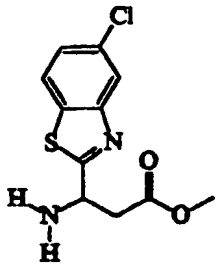
[0069] Compound Nr. 9 was obtained with a procedure and preparative scale analogous to that described in example 1, starting from the ester methyl RS-3-amino-3-(5-chlorobenzothiazol-2-yl)propanoate with an overall yield of 68%.

[0070] The physico-chemical characterization of compound Nr. 9 gave the following results:

Elemental analysis [% found (theoretical)] =
C 52.73 (52.68); H 5.72 (5.75); N 9.12 (9.22); Cl 7.72 (7.78); S 6.97 (7.03).

b) Preparation of methyl (±)RS-3-amino-3-(5-chlorobenzothiazol-2-yl)propanoate

[0071]



[0072] The ester methyl RS-3-amino-3-(5-chlorobenzothiazol-2-yl)propanoate was obtained with a procedure analogous to that described in example 5 for the ester methyl RS-3-amino-3-(benzothiazol-2-yl)propanoate.

GC-MS: 270(M^+), 211, 197(100%), 170, 102, 70

EXAMPLE 6

Determination of the fungicidal effectiveness against peronospora *(Plasmopara viticola)* of compounds having formula (I) and (II) in preventive leaf application.

[0073] Cultivar Dolcetto vine leaves, grown in vases in a conditioned environment (20±1°C), 70% relative humidity), are treated by spraying both sides of the leaves with compounds 1-7 dispersed in a hydroacetone solution at 20% by volume of acetone.

[0074] After remaining 24 hours in a conditioned environment, the plants are sprayed on both sides of the leaf with an aqueous suspension of conidia of *Plasmopara viticola* (200,000 conidia per cm^3).

[0075] The plants are kept in a humidity saturated environment, at 21°C, for the incubation period of the fungus and, at the end of this period (7 days), the fungicidal activity is evaluated according to an evaluation percentage scale from 100 (healthy plant) to 0 (completely infected plant).

[0076] The data obtained with compounds 1-8 and with the reference compounds are indicated in Table 1 below.

Table 1

Antiperonosporic effectiveness in preventive leaf application on vines	Effectiveness expressed as leaf diffusion control % of the disease with respect to a non-treated reference sample and with the following doses			
	Dose (g/hl)			
Compound	30	7.5	1.8	0.45
1	100	100	100	80
2	100	100	100	100
3	100	100	85	65
4	100	100	100	75
5	100	100	90	70
6	100	100	92	65
7	100	100	90	67
8	100	100	92	70
9	100	100	100	90

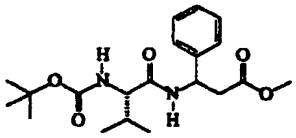
Table 1 (continued)

Antiperonosporic effectiveness in preventive leaf application on vines	Effectiveness expressed as leaf diffusion control % of the disease with respect to a non-treated reference sample and with the following doses			
	Dose (g/hl)			
Compound	30	7.5	1.8	0.45
Reference 1	100	90	20	0
Reference 2	100	88	65	30
Reference 3	100	91	55	10
Reference 4	90	75	55	15
Reference 5	96	75	15	0

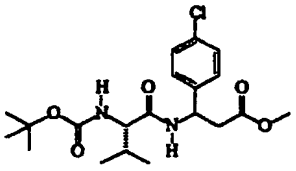
List of references indicated in Tables 1a-b

[0077]

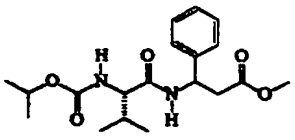
Reference 1 (EP 0 718 280 A2, compound Nr. 4.4):



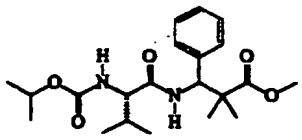
Reference 2 (EP 0 718 280 A2, compound Nr. 4.10):



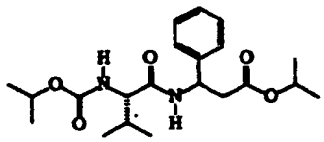
Reference 3 (EP 0 718 280 A2, compound Nr. 16.6):



Reference 4 (EP 0 718 280 A2, compound Nr. 16.9):

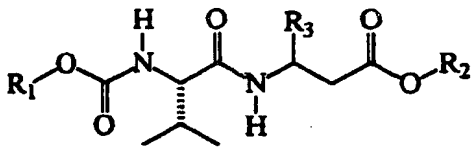


Reference 5 (EP 0 652 229 A2, compound Nr. 58):



Claims

1. Dipeptide compounds having general formula (I):



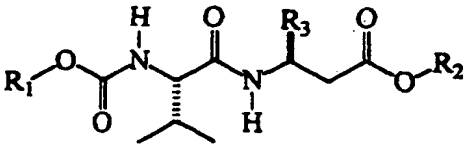
(I)

wherein:

- R_1 represents an isopropyl or phenyl group;
- R_2 represents a methyl group;
- R_3 can be a phenyl group substituted in position 4 with an R_4 group; or it can represent a 2-benzothiazole group, optionally substituted with an R_5 group;
- R_4 and R_5 can be a fluorine or chlorine atom; a methyl or ethyl group; or a methoxyl group; or they can represent a cyano group.

2. Dipeptide compounds having general formula (I) wherein the diastereoisomeric forms S-S or S-R, in which the first letter refers to the chiral centre of valine and the second to the chiral centre of aromatic β-amino acid, are present in any molar ratio.

3. Dipeptide compounds having general formula (I) wherein the absolute configuration of the chiral atom of Valine is S and that of aromatic β-amino acid is R, as represented by general formula (II):



(II)

wherein:

- R_1, R_2, R_3 have the meaning defined in claim 1.

4. Compound according to claim 1, consisting of methyl RS-[3-(N-isopropoxycarbonyl-S-valinyl)amino]-3-(4-chlorophenyl)propanoate.

5. Compound according to claim 1, consisting of methyl R-[3-(N-isopropoxycarbonyl-S-valinyl)amino]-3-(4-chlorophenyl)propanoate.

6. Compound according to claim 1, consisting of methyl S-[3-(N-isopropoxycarbonyl-S-valinyl)amino]-3-(4-chlorophenyl)propanoate.

7. Compound according to claim 1, consisting of methyl RS-[3-(N-isopropoxycarbonyl-S-valinyl)amino]-3-(4-methylphenyl)propanoate.

8. Compound according to claim 1, consisting of methyl RS-[3-(N-phenoxycarbonyl-S-valinyl)amino]-3-(4-ethylphenyl)propanoate.

9. Compound according to claim 1, consisting of methyl RS-[3-(N-isopropoxycarbonyl-S-valinyl)amino]-3-(4-methoxyphenyl)propanoate.

10. Compound according to claim 1, of methyl RS-[3-(N-isopropoxycarbonyl-S-valinyl)amino]-3-(4-cyano-phenyl) propanoate.

11. Compound according to claim 1, consisting of methyl RS-[3-(N-isopropoxycarbonyl-S-valinyl)amino]-3-(benzothiazol-2-yl)propanoate.

12. Compound according to claim 1, consisting of methyl RS-[3-(N-isopropoxycarbonyl-S-valinyl)amino]-3-(5-chlorobenzothiazol-2-yl)propanoate.

13. Use of the dipeptide compounds according to the previous claims for the control of phytopathogens in the agronomic field.

14. Fungicidal compositions comprising solid carriers, liquid diluents, surface-active agents or other special additives and at least one of the compounds according to claims 1 to 12.

15. The fungicidal compositions according to claim 14, comprising one or more fungicides selected from:

(1) Cymoxanil corresponding to 1-(2-cyano-2-methoxyimino-acetyl)-3-ethylurea;
(2) Fosetyl-Al corresponding to the aluminum salt of ethyl hydrogen phosphonate;
(3) Potassium phosphonate;
(4) Benalaxyl corresponding to methyl N-(phenylacetyl)-N-2,6-xylyl-RS-alaninate;
(5) Methyl N-(phenylacetyl)-N-2,6-xylyl-R-alaninate;
(6) Metalaxyl corresponding to methyl N-(2-methoxyacetyl)-N-2,6-xylyl-RS-alaninate;
(7) Mefenoxam corresponding to methyl N-(2-methoxyacetyl-N-2,6-xylyl-R-alaninate;
(8) Oxadixyl corresponding to 2-methoxy-N-(2-oxo-1,3-oxazolidin-3-yl)acet-2',6'-xylidinide;
(9) Ofurace corresponding to DL-3-[N-chloroacetyl-N-(2,6-xylyl)-amino]-γ-butyrolactone;
(10) Iprovalicarb corresponding to O-(1-methylethyl)-N-[2-methyl-1-[[[1-(4-methylphenyl)ethyl]amino]carbo-

nyl]propyl]carbamate;
(11) Azoxystrobin corresponding to methyl (E)-2-[2-[6-(2-cyanophenoxy)-pyrimidin-4-yloxy]phenyl]-3-methoxy-acrylate;
(12) Kresoxym-methyl corresponding to methyl (E)-methoxyimino-α-[o-tolyloxy)-o-tolyl]acetate;
(13) Metominofen corresponding to the experimental abbreviation SSF-126 and corresponding to N-methyl-(E)-methoxyimino-(2-phenoxyphenyl)acetamide;
(14) Acylbenzolar corresponding to methylbenzothiadiazole-7-thiocarboxylate;
(15) Famoxadone corresponding to 5-methyl-5-(4-phenoxyphenyl)-3-(phenylamino)oxazolidin-2,4-dione;
(16) Fenamidone corresponding to 4-methyl-4-phenyl-1-(phenylamino)-2-methylthioimidazolidin-5-one;
(17) IKF916 corresponding to 2-cyano-4-chloro-5-(4-methylphenyl)-1-(N,N-dimethylaminosulfamoyl) imidazole;
(18) Fluazinam corresponding to 3-chloro-N-(3-chloro-5-trifluoromethyl-2-pyridyl)-α,α,α-trifluoro-2,6-dinitro-*p*-toluidine;
(19) Dimethomorph corresponding to (E,Z)-4-[3-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl)acryloyl] morpholine;
(20) Flumetover corresponding to N,N-diethylamide of 4-trifluoromethyl-6-(3,4-dimethoxyphenyl)benzoic acid;
(21) Chlorothalonil corresponding to 1,3-dicyano-2,4,5,6-tetrachlorobenzene;
(22) Thiram corresponding to *bis*-(dimethylthiocarbamoyl)disulfide (polymer);
(23) Propineb corresponding to the zinc salt of propylene*bis*(dithiocarbamate) (polymer);
(24) Mancozeb corresponding to the manganese and zinc salt of ethylene*bis*(dithiocarbamate)(polymer);
(25) Maneb corresponding to the manganese salt of ethylene*bis*(dithiocarbamate) (polymer);
(26) Zineb corresponding to the zinc salt of ethylene*bis*(dithiocarbamate) (polymer);
(27) Dichlofluanide corresponding to N-dichlorofluoromethylthio-N',N'-dimethyl-N-phenylsulf amide;
(28) Tolylfluanide corresponding to N-dichlorofluoromethylthio-N',N'-dimethyl-N-p-tolylsulfamide;
(29) Captano corresponding to N-(trichloromethylthio)cyclohex-4-ene-1,2-dicarboxyimide;
(30) Folpet corresponding to N-(trichloromethylthio)phthalimide;
(31) Dithianon corresponding to 5,10-dihydro-5,10-dioxonaphthol[2,3-b]-1,4-dithi-in-2,3-dicarbonitrile;
(32) Etridiazole corresponding to ethyl-3-trichloromethyl-1,2,4-thiadiazolyl ether;
(33) Hymexanol corresponding to 5-methylisoxazol-3-ole;
(34) Protiocarb corresponding to S-ethyl-(3-dimethylaminopropyl)thiocarbamate;
(35) Propamocarb corresponding to propyl-(3-dimethylaminopropyl)carbamate;
(36) A copper (I) salt or copper (II) salt, such as copper oxychloride, copper hydroxide, or copper sulfate;
(37) Mepanipyrim corresponding to N-(4-methyl-6-prop-1-inylpyrimidin-2-yl)aniline;
(38) Pirymethanil corresponding to N-(4,6-dimethylpyrimidin-2-yl)aniline;
(39) Cyprodinil corresponding to N-(4-methyl-6-cyclopropylpyrimidin-2-yl)aniline;
(40) R-3-aminobutanoic acid or RS-3-aminobutanoic acid.

16. The compositions according to claim 14, wherein other phytoregulators, antibiotics, herbicides, insecticides, fertilizers are present.

17. The compositions according to claim 14, wherein the concentration of the compounds having formula (I) varies from 0.5 to 90%.

18. A process for the preparation of the compositions according to claim 14, wherein the active substance is dissolved by means of a solvent medium and/or solid diluent, optionally in the presence of surface-active agents.

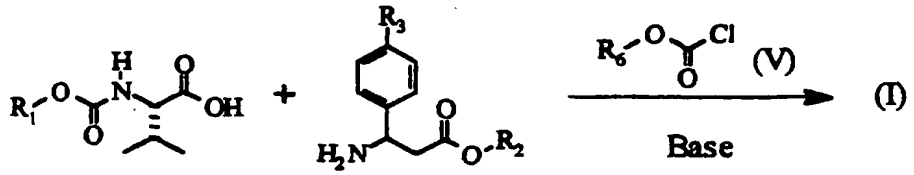
19. A method for fighting fungine infections consisting in applying the fungicide compositions according to claims 14-17, on all parts of the plant, on the aerial parts (leaves, stems, shoots, branches), on the hypogeous parts for controlling typical root pathogens, or on the seeds themselves before sowing, or on the ground where the plant grows.

20. The method according to claim 19, wherein the active compounds are distributed on the ground with the following doses per hectare:

- 5-500 g of compound having formula (I);
- 5-3500 g of each fungicide from (1)-(40) as defined in claim 15.

21. A process for the preparation of the compounds having formula (I) wherein the following synthetic method is followed:

Scheme A:



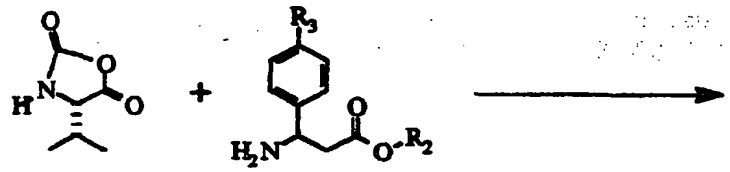
(III) (IV)

wherein:

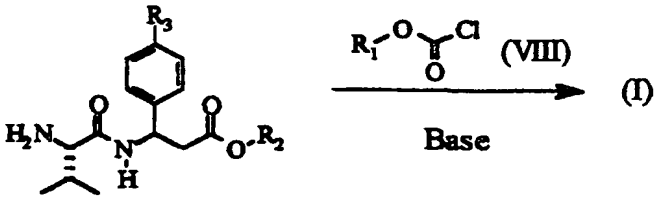
the carbamate (III) is reacted with an organic base, in an organic solvent, at a temperature ranging from -40°C to 25°C;
the alkyl chloroformiate (V), wherein R_6 has the meaning of a linear or branched C_1-C_8 alkyl group, is added to the reaction within a temperature range of -40°C to 25°C;
the ester (IV), optionally diluted in the reaction solvent, is added to the reaction, the temperature being maintained within a range of -40°C to 30°C, to obtain the compounds having formula (I);
R_1, R_2 and R_3 have the meanings already defined in claim 1.

22. A process for the preparation of the compounds having formula (I) wherein the following synthetic method is followed:

Scheme B:



(VI) (IV)



(VII)

wherein:

the ester (IV) is reacted with the anhydride (VI), in an organic solvent, optionally in the presence of an organic base, at a temperature ranging from -80°C to room temperature;
the dipeptide (VII) thus obtained is reacted, in an organic solvent, with the chloroformiate (VIII) in the presence

of an inorganic base or organic base, at a temperature ranging from -40°C to 30°C, to obtain the compound having formula (I).

23. The process according to claim 21 or 22, wherein the optically active ester having formula IV enriched in one of the enantiomeric forms R or S, is used.

24. The process according to claim 23, wherein the ester having formula IV is obtained by the fractional crystallization of the salt formed by the reaction of the racemic ester (IV) with a suitable optically active acid.

25. The process according to claim 23, wherein the ester having formula IV is obtained by the enantioselective enzymatic hydrolysis of the racemic ester (IV).

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 99 20 3955

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X	EP 0 718 280 A (ISAGRO RICERCA S.R.L., ITALY) 26 June 1996 (1996-06-26)	1-25	C07K5/06
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Place of search	Date of completion of the search	Examiner
MUNICH	19 June 2000	Kronester-Frei, A

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